Amendments to the Claims

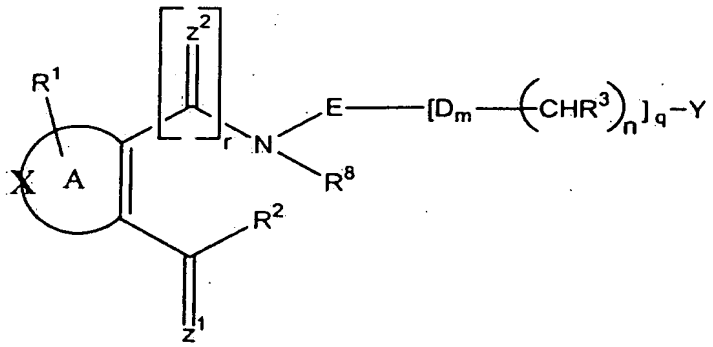
This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

Claim 1 (Withdrawn-Amended): A compound capable of binding to the ubiquinone binding site of DHODH which contains an aromatic or non-aromatic ring system as a core structure, a group capable of forming a hydrogen bond and/or interacting ionically with structural elements of subsite 2 or 3 of the ubiquinone binding site of DHODH and a group capable of interacting hydrophobically with structural elements of subsite 1 of the ubiquinone binding site of DHODH

with the proviso that the following compounds are excluded:

compounds of the ~~general~~ formula



wherein

A is a non-aromatic ring system containing five carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring can be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO or SO_2, and wherein one or more of the carbon atoms of the ring can carry a substituent R^1;

D is O, S, SO_2, NR^4, or CH_2;

Z^1 and Z^2 are independent from each other O, S, or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy or alkyl;

R^2 is H, OR^6, or NHR^7

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl, O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, or S-cycloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl, or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl, or aryl;

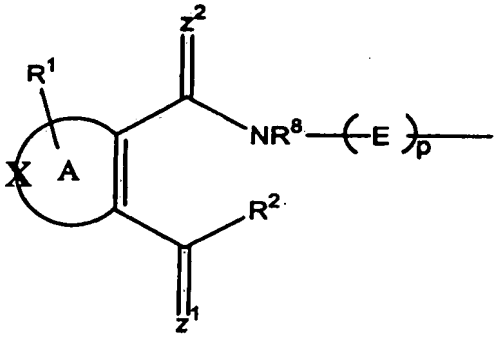
R^6 is H, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester, or dialkylphosphate;

R^7 is H, alkyl, aryl, alkoxy, O-aryl, cycloalkyl, or O-cycloalkyl;

R^8 is hydrogen or alkyl;

E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



m is 0 orl;

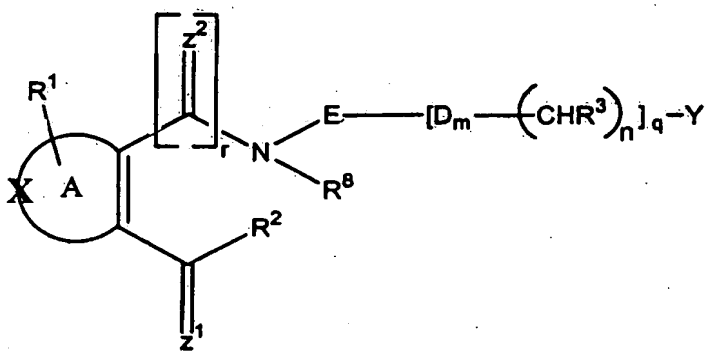
n is 0 orl;

p is 0 or 1;

r is 0 or 1; and

q is 0 to 10;

and compounds of the general formula



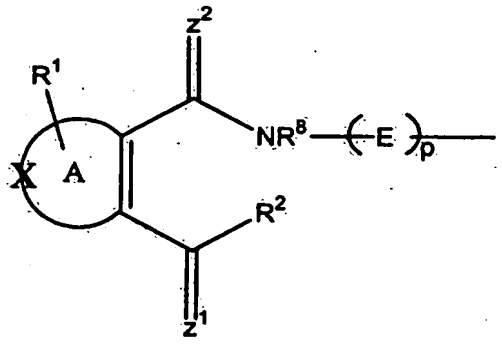
wherein

A is a non-aromatic ring system containing 4, 6, 7 or 8 carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring can be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO or SO^2, and wherein one or more of the carbon atoms of the ring can carry a substituent R^1;

D, Z^1, Z^2, R^1, R^3, R^4, R^5, R^6, R^8, and E are as defined above,

R^2 is H, or OR^6;

Y is a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



wherein m, n, p, r, and q are as defined above.

Claim 2 (Withdrawn): The compound of claim 1 wherein the non-aromatic ring system is a monocyclic ring.

Claim 3 (Withdrawn): The compound of claim 1 wherein the non-aromatic ring system is a 5-membered ring.

Claim 4 (Withdrawn): The compound of claim 1 wherein the 5-membered ring is a cyclopentene ring.

Claim 5 (Withdrawn): The compound of claim 1 wherein the group connecting the core with the hydrophobic group is bonded to the carbon atom participating in the double bond of the cyclopentene ring.

Claim 6 (Withdrawn): The compound of claim 1 wherein the non-aromatic ring system is an optionally substituted ring system containing 4 to 8 carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring may be substituted by a group X, wherein X is selected from the group

consisting of S, O, N, NH, NHR, SO or SO_2 and R is an alkyl group or an unsaturated or saturated carbocycle.

Claim 7 (Withdrawn): The compound of claim 1 wherein the non-aromatic ring system is a condensed ring system comprising a 5-membered non-aromatic ring and a 6-membered aromatic or non-aromatic ring.

Claim 8 (Withdrawn): The compound of claim 7 wherein the 6-membered ring contains one or two nitrogen atoms as heteroatom(s).

Claim 9 (Withdrawn): The compound of claim 8 wherein the group connecting the core with the hydrophobic group is bonded to said nitrogen heteroatom or one of said nitrogen atoms.

Claim 10 (Withdrawn): The compound of claim 1 wherein the group capable of forming a hydrogen bond and/or interacting ionically with structural elements of subsite 2 or 3 is capable of binding alternatively to said subsite 2 or subsite 3.

Claim 11 (Withdrawn): The compound of claim 1 containing an additional group capable of forming a hydrogen bond and/or ionically interacting with structural elements of subsite 2 or 3.

Claim 12 (Withdrawn): The compound of claim 1 containing an additional group capable of forming a hydrogen bond and/or ionically interacting with structural elements of

subsite 2 or 3 and wherein one group is capable of interacting with subsite 2 and the other group is capable of interacting with subsite 3.

Claim 13 (Withdrawn): The compound of claim 1 wherein the group capable of forming a hydrogen bond and/or interacting ionically with structural elements of subsite 2 or 3 is capable of binding to said subsite 3 only.

Claim 14 (Withdrawn): A compound capable of binding to the ubiquinone binding site of DHODH which contains a ring system as a core structure, a group capable of forming a hydrogen bond and/or interacting ionically with residues His 56 and/or Tyr 356 of subsite 3 of the ubiquinone binding site of DHODH and a group capable of interacting hydrophobically with structural elements of subsite 1 of the ubiquinone binding site of DHODH.

Claim 15 (Withdrawn): The compound of claim 14 wherein the group capable of interacting with subsite 3 of DHODH forms a hydrogen bond with residue Tyr 147 of subsite 3 of DHODH.

Claim 16 (Withdrawn): The compound of claim 14 wherein the group capable of forming a hydrogen bond and/or interacting ionically is capable of binding to said subsite 3 only.

Claim 17 (Withdrawn): The compound of claim 14 additionally containing a group capable of forming a hydrogen bond and/or interacting ionically with subsite 2 of the ubiquinone binding site of DHODH.

Claim 18 (Withdrawn): The compound of claim 14 wherein the ring system is an aromatic ring system.

Claim 19 (Withdrawn): The compound of claim 1 which is crystallizable with DHODH.

Claim 20 (Withdrawn): The compound of claim 1 wherein the group connecting the core with the hydrophobic group is selected from -NH-, -O-, -CO-, -NHCONH-, -NHCO- and - CONH-.

Claim 21 (Withdrawn-Amended): The compound of claim 1 wherein the group capable of interacting with subsite 2 and/or 3 of DHODH is at least one group selected from the group consisting of $-SO_3H$, -OH, $-NO_2$, -CN, CF_3, ~~=0~~ -O, and ~~-COON~~ -COOH.

Claim 22 (Withdrawn): The compound of claim 1 wherein the group capable of interacting with subsite 2 or 3 of DHODH is an anion.

Claim 23 (Withdrawn): The compound of claim 1 wherein the group capable of interacting with subsite 2 or 3 of DHODH is a carboxylic group.

Claim 24 (Withdrawn): The compound of claim 1 wherein the group capable of interacting with subsite 2 or 3 of DHODH is an anion which interacts with residues Gln 47 and/or Arg 136 of subsite 2 of DHODH.

Claim 25 (Withdrawn): The compound of claim the group capable of interacting with subsite 2 or 3 of DHODH is a carboxylic group which is a substituent of the ring system.

Claim 26 (Withdrawn): The compound of claim 1 wherein the hydrophobic group is capable of interacting with the hydrophobic pocket of subsite 1 of DHODH comprising amino acid residues Leu 142, Met 43, Leu 46, Ala 55, Ala 59, Phe 98, Met 111, Leu 359, and Pro 364.

Claim 27 (Withdrawn): The compound of claim 1 wherein the hydrophobic group is selected from optionally substituted monocyclic or bicyclic aryl groups.

Claim 28 (Withdrawn): The compound of claim 1 wherein the hydrophobic group is an optionally substituted biphenyl group.

Claim 29 (Withdrawn): The compound of claim 1 wherein the hydrophobic group is an optionally substituted benzyl phenyl ether group.

Claim 30 (Withdrawn): The compound of claim 1 wherein the hydrophobic group has at least one substituent selected from the group consisting of F, Cl, Br, I, CF_3, OCF_3, and OCH_3.

Claim 31 (Withdrawn): The compound of claim 1 wherein the DHODH is human DHODH consisting of amino acids Met30 to Arg396.

Claim 32 (Withdrawn): The compound of claim 1 having an IC50 value in the DHODH activity test of less than 500 nM.

Claim 33 (Withdrawn): The compound of claim 1 having an IC50 value of less than 300 nM.

Claim 34 (Withdrawn): The compound of claim 1 having an IC50 value of less than 100 nM.

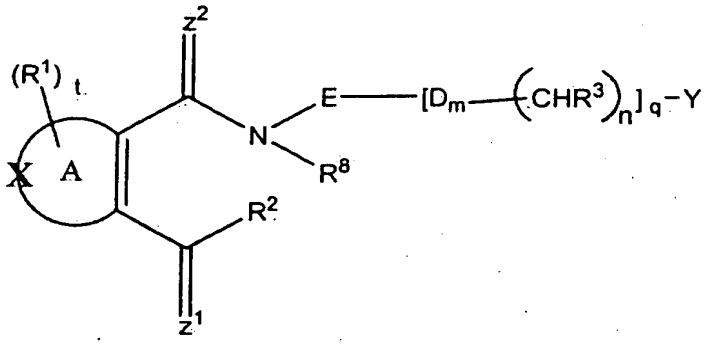
Claim 35 (Withdrawn-Amended): ~~A~~ The compound of claim 1 which inhibits the proliferation of human PBMC's by more than 50 % with ~~and~~ an IC50 of less than 100 μM.

Claim 36 (Withdrawn-Amended): The compound of claim 1 which inhibits the proliferation of human PBMC's by more than 50 % with ~~and~~ an IC50 of less than 50 μM

Claim 37 (Withdrawn-Amended): The compound of claim 1 which inhibits the proliferation of human PBMC's by more than 50 % with ~~and~~ an IC50 of less than 10 μM.

Claim 38 (Withdrawn-Amended): The compound of claim 1 which inhibits the proliferation of human PBMC's by more than 50 % with ~~and~~ an IC50 of less than 5 μM.

Claim 39 (Withdrawn-Amended): The compound of claim 1 which is a compound of ~~the general~~ formula (I)



or salts or ~~isomeres~~ isomers thereof, wherein

A is a 4-8 membered non-aromatic ring system, wherein one or more of the carbon atoms in the ring can be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO, CO or SO_2;

D is O, S, SO_2, NR^4 or CH_2;

Z^1 and Z^2 are independent from each other O, S, or NR^5;

R^1 independently represents H, halogen, haloalkyl, haloalkyloxy $-CO_2R"$, $-SO_3H$, -OH, -CONR*R", -CR"O, $-SO_2$-NR*R", $-NO_2$, $-SO_2$-R", -SO-R*, -CN, alkoxy, alkylthio, aryl, -NR"-CO_2-R', -NR"-CO-R*, ~~-NR"-S02-R'~~ -NR"-SO_2-R', - O-CO-R*, -NR*R", -NR*OR"-O-CO_2-R*, -O-CO-NR*R"; cycloalkyl, alkylamino, hydroxyalkylamino, -SH, heteroaryl, or alkyl;

R* independently represents H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroaryl;

R' independently represents H, $-CO_2R"$, -CONHR", -CR"O, $-SO_2NR"$-~~CO-haloalkyl~~ -NR"-CO-haloalkyl, $-NO_2$, -NR"-SO_2-haloalkyl, -NR"-SO_2-alkyl, $-SO_2$-alkyl, -NR"-CO-alkyl, -CN, alkyl, cycloalkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, -

NR"R*, -NR"OR*, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R" independently represents hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is H, OR^6, NHR^7, or R^2 togehter with the nitrogen atom to which R^8 is attached forms a 5 or 6 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_{0-3}$ and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl; O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, or S-cycloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl, or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl, or aryl;

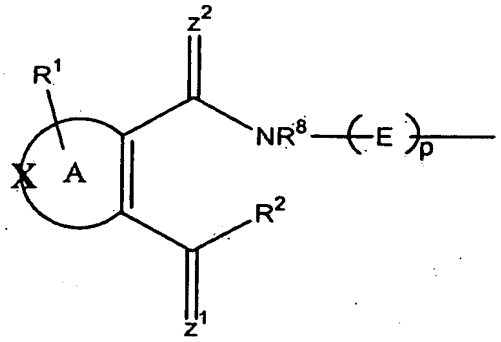
R^6 is H, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester, or dialkylphosphate;

R^7 is H, alkyl, aryl, alkoxy, O-aryl, cycloalkyl, or O-cycloalkyl;

R^8 is hydrogen or alkyl;

E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



m is 0 or 1;

n is 0 or 1;

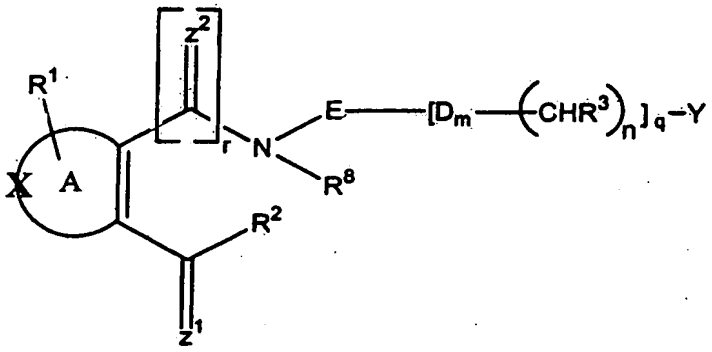
p is 0 or 1;

q is 0 or 1;

t is 1 to 3;

with the proviso that trans-2-[4-(Naphthalin-2-yl)thiazol-2-ylaminocarbonyl]cyclopentane carboxylic acid is excluded.

Claim 40 (Withdrawn-Amended): The compound of claim 1 which is a compound of the general formula (II)



or salts or isomeres thereof, wherein

A is a 3-8 membered non-aromatic ring system, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring can be

replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO, CO or SO_2, wherein, when r = 0,

there is no double bond between the carbon atoms carrying the substituents $-CZ^1-$ and $-CZ^2-$;

D is O, S, SO_2, NR^4 or CH_2;

Z^1 and Z^2 are independent from each other O, S, or NR^5;

R^1 independently represents H, halogen, haloalkyl, haloalkyloxy $-CO_2R"$, $-SO_3H$, -OH, -CONR*R", -CR"O, $-SO_2-NR*R"$, $-NO_2$, $-SO_2-R"$, -SO-R*, -CN, alkoxy, alkylthio, aryl, $-NR"-CO_2-R'$, -NR"-CO-R*, $-NR"-SO_2-R'$, - O-CO-R*, -NR*R", -NR*OR"-O-CO_2-R*, -O-CO-NR*R"; cycloalkyl, alkylamino, hydroxyalkylamino, -SH, heteroaryl, or alkyl;

R* independently represents H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, - SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroaryl;

R' independently represents H, $-CO_2R"$, -CONHR", -CR"O, $-SO_2NR"$, - NR"-CO-haloalkyl, $-NO_2$, $-NR"-SO_2$-haloalkyl, $-NR"-SO_2$-alkyl, $-SO_2$-alkyl, -NR"-CO-alkyl, -CN, alkyl, cycloalkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, -NR"R*, -NR"OR*, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R" independently represents hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is H, OR^6, NHR^7, $NHOR^6$ or R^2 ~~togehter~~ together with the nitrogen atom to which R^8 is attached forms a 5 or 6 membered heterocyclic ring with the proviso that R^2 is $[CH_2]_{0-3}$ and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl; O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, or S-cycloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl, or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl, or aryl;

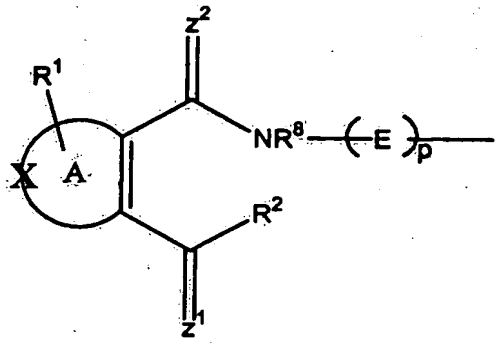
R^6 is H, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester, or dialkylphosphate;

R^7 is H, alkyl, aryl, alkoxy, O-aryl, cycloalkyl, or O-cycloalkyl;

R^8 is hydrogen or alkyl;

E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



m is 0 or 1;

n is 0 or 1;

p is 0 or 1;

r is 0 or 1; and

q is 0 or l;

t is 1 to 3;

Claim 41 (Withdrawn): The compound according to claim 39, wherein R' is selected from the group consisting of OH, CO_2H and SO_3H.

Claim 42 (Withdrawn): The compound according to claim 39, wherein both Z^1 and Z^2 are O.

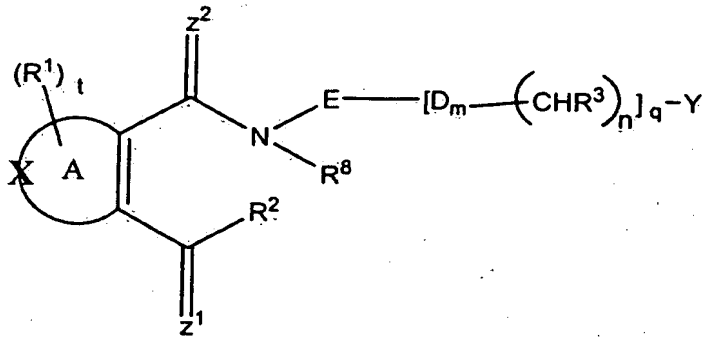
Claim 43 (Withdrawn-Amended): The compound according to claim 39, wherein E is selected from the group consisting of phenyl, ~~1-naphtyl~~ 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl and is optionally substituted with one or more substituents R'.

Claim 44 (Withdrawn): The compound according to claim 39, wherein q=0, t=1, A is a carbocyclic non-aromatic ring system, Y is H or F, and E is phenyl which is optionally substituted with at least one substituent selected from the group consisting of Cl, F, CF_3, OCF_3, O-methyl and O-ethyl.

Claim 45 (Withdrawn): The compound according to claim 39, wherein q=0, t=1, A is a carbocyclic non-aromatic ring system, and E and Y are phenylene and phenyl, respectively, wherein E is optionally substituted with at least one substituent selected from the group consisting of Cl and F and Y is optionally substituted with at least one substituent selected from the group consisting of O-methyl, O-ethyl, OCF_3, Cl and F.

Claim 46 (Withdrawn): The compound according to claim 39, wherein Y and -NCR^8 are in para position on E.

Claim 47 (Withdrawn-Amended): A compound of the general formula (11) and salts and physiologically functional derivatives thereof,



wherein

A is a heteroaromatic 5-membered ring system containing one or more groups X selected from the group consisting of S, O, N, NR^4, SO_2 and SO;

D is O, S, SO_2, ~~NW~~ NR^4, or ~~CH2~~ CH_2;

Z^1 and Z^2 are independent from each other and are O, S, or NR^5;

R^1 independently represents H, halogen, haloalkyl, haloalkyloxy $-CO_2R''$, $-SO_3H$, -OH, -CONR*R", -CR"O, $-SO_2$-NR*R", $-NO_2$, $-SO_2$-R", -SO-R*, -CN, alkoxy, alkylthio, aryl, -NR" $-CO_2$-R', -NR"-CO-R*, -NR"-SO_2-R', - O-CO-R*, -O-CO_2-R*, -O-CO-NR*R"; cycloalkyl, alkylamino, hydroxyalkylamino, -SH, heteroaryl, or alkyl;

R* independently represents H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, - SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroaryl;

R' independently represents H, $-CO_2R''$, -CONHR", -CR"O, $-SO_2NR''$, - NR"-CO-haloalkyl, $-NO_2$, -NR"-SO_2-haloalkyl, -NR"-SO_2-alkyl, $-SO_2$-alkyl, -NR"-CO-alkyl, -CN, alkyl, cycloalkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R" independently represents hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is H or OR^6, ~~NHR'~~ $\underline{NHR^7}$, ~~NWOR'~~ $\underline{NR^7OR^7}$ or R^2 togehter with the nitrogen atom which is attached to R^8 form a 5 or 6 membered heteroyclic ring with the proviso that R^2 is -~~[CH2]~~$_s$ $\underline{[CH_2]_s}$ and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, alkoxy, O-aryl; O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl; S-cycloalkyl, arylalkyl, or haloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, ~~0-aryl~~ $\underline{O\text{-aryl}}$, alkyl or aryl;

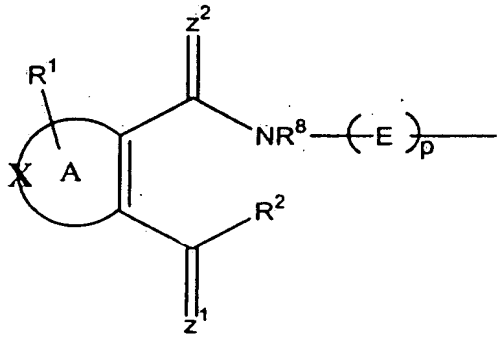
R^6 is H, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester, or dialkylphosphate;

R^7 is H, OH, alkyl, aryl, alkoxy, O-aryl, cycloalkyl, or O-cycloalkyl;

R^8 is hydrogen, or alkyl;

E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



m is 0 or 1;

n is 0 or 1;

p is 0 or 1;

q is 0 or 1;

s is 0 to 2; and

t is 0 to 3;

with the proviso that the following compounds are excluded:

compounds wherein ring A contains five atoms, ~~$Z^1=Z^2=O$~~ $Z^1=Z^2=O$, and R^2 ~~togehter~~ together with the nitrogen atom which is attached to R^8 forms a 5 membered heteroyclic ring with the proviso that R^2 is ~~$[CH2]_s$~~ $[CH_2]_s$, R^8 is absent and s is 0;

compounds wherein ring A contains three carbon atoms and two nitrogen atoms, ~~$Z^1=Z^2=O$~~ $Z^1=Z^2=O$, and R^2 togehter with the nitrogen atom which is attached to R^8 form a 5 membered heteroyclic ring with the proviso that R^2 is ~~$[CH2]_s$~~ $[CH_2]_s$, R^8 is absent and s is 0;

4-[4-(naphthalin-2-yl) thiazol-2-ylaminocarbonyl]-furan-3-carboxylic acid; and

5-[4-(naphthalin-2-yl]thiazol-2-ylaminocarbonyl]-2H-[1,2,3]-triazole-4-carboxylic acid.

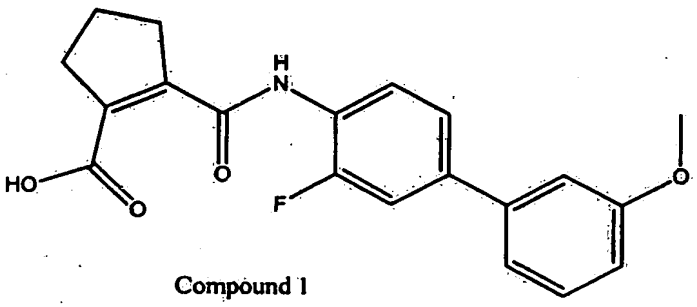
Claim 48 (Withdrawn): A crystal containing a polypeptide and a compound of claim 1 wherein the polypeptide includes a ubiquinone binding site of DHODH.

Claim 49 (Withdrawn): A crystal containing a polypeptide and a compound of claim 39 wherein the polypeptide includes a ubiquinone binding site of DHODH.

Claim 50 (Withdrawn): A crystal containing a polypeptide and a compound of claim 40 wherein the polypeptide includes a ubiquinone binding site of DHODH.

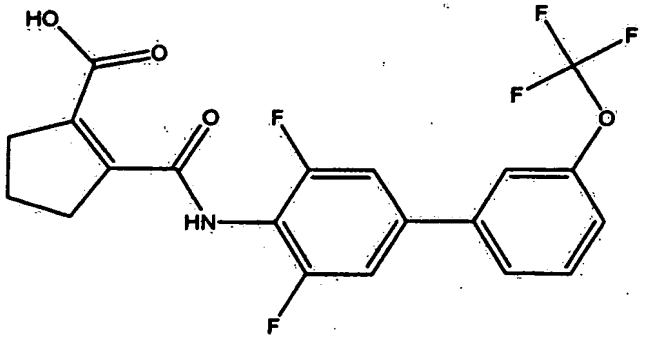
Claim 51 (Withdrawn): A crystal containing a polypeptide and a compound of claim 47 wherein the polypeptide includes a ubiquinone binding site of DHODH.

Claim 52 (Withdrawn): The crystal of claim 48 wherein the compound is compound 1



Compound 1

Claim 53 (Withdrawn): The crystal of claim 48 wherein the compound is compound 2



Compound 2

Claim 54 (Withdrawn): The crystal of claim 48 wherein no salt bridge or hydrogen bridge is formed between the compound and an amino acid residue in subsite 2 of DHODH.

Claim 55 (Withdrawn): The crystal of claim 48 wherein no salt bridge or hydrogen bridge is formed between the carboxylic group of Compound 1 or Compound 2 and the sidechain of Arg 136.

Claim 56 (Withdrawn): The crystal of claim 48 wherein the compound forms a hydrogen bond and/or interacts ionically with structural elements of subsite 3 only.

Claim 57 (Withdrawn): The crystal of claim 48 wherein the compound forms hydrogen bond(s) with residues His 56 and/or Tyr 356 of subsite 3 of DHODH.

Claim 58 (Withdrawn): The crystal of claim 48 wherein the compound forms a hydrogen bond with residue Tyr 147 of subsite 3 of DHODH.

Claim 59 (Withdrawn): A method of identifying a compound which is an inhibitor of DHODH comprising the steps of

(a) obtaining the atomic coordinates of the crystal of claim 48;

(b) using said atomic coordinates to define the ubiquinone binding site of DHODH; and

(c) identifying a compound which fits the ubiquinone binding site of DHODH.

Claim 60 (Withdrawn): A method of identifying a compound which is an inhibitor of DHODH comprising the steps of

(d) obtaining the atomic coordinates of the crystal of claim 49;

(e) using said atomic coordinates to define the ubiquinone binding site of DHODH; and

(f) identifying a compound which fits the ubiquinone binding site of DHODH.

Claim 61 (Withdrawn): A method of identifying a compound which is an inhibitor of DHODH comprising the steps of

(g) obtaining the atomic coordinates of the crystal of claim 50;

(h) using said atomic coordinates to define the ubiquinone binding site of DHODH; and

(i) identifying a compound which fits the ubiquinone binding site of DHODH.

Claim 62 (Withdrawn): A method of identifying a compound which is an inhibitor of DHODH comprising the steps of

(j) obtaining the atomic coordinates of the crystal of claim 51;

(k) using said atomic coordinates to define the ubiquinone binding site of DHODH; and

(1) identifying a compound which fits the ubiquinone binding site of DHODH.

Claim 63 (Withdrawn): A method of identifying a compound which is an inhibitor of DHODH comprising the steps of

(m)obtaining the atomic coordinates of the crystal of claim 48;

(n) using said atomic coordinates to define the structural requirements of the inhibitor contained in the polypeptide-inhibitor complex; and

(o) designing a compound on the basis of said structural requirements.

Claim 64 (Withdrawn): A method of identifying a compound which is an inhibitor of DHODH comprising the steps of

(p) obtaining the atomic coordinates of the crystal of claim 49;

(q) using said atomic coordinates to define the structural requirements of the inhibitor contained in the polypeptide-inhibitor complex; and

(r) designing a compound on the basis of said structural requirements.

Claim 65 (Withdrawn): A method of identifying a compound which is an inhibitor of DHODH comprising the steps of

(s) obtaining the atomic coordinates of the crystal of claim 50;

(t) using said atomic coordinates to define the structural requirements of the inhibitor contained in the polypeptide-inhibitor complex; and

(u) designing a compound on the basis of said structural requirements.

Claim 66 (Withdrawn): A method of identifying a compound which is an inhibitor of DHODH comprising the steps of

(v) obtaining the atomic coordinates of the crystal of claim 51;

(w) using said atomic coordinates to define the structural requirements of the inhibitor contained in the polypeptide-inhibitor complex; and

(x) designing a compound on the basis of said structural requirements.

Claims 67-74. (Canceled)

Claim 75 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 1, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 76 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 39, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 77 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 40, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 78 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 47, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 79 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 67, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 80 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 68, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 81 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 69, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 82 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 70, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 83 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 71, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 84 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 72, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 85 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 73, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 86 (Withdrawn): A method for treatment of a disease or a therapeutic indication in which inhibition of dihydrooratate dehydrogenase is beneficial which comprises administering to a mammal an effective amount of a compound according to claim 74, a physiologically functional derivative or a pharmacologically tolerable salt thereof.

Claim 87 (Withdrawn): The method of claim 75 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 88 (Withdrawn): The method of claim 76 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 89 (Withdrawn): The method of claim 77 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 90 (Withdrawn): The method of claim 78 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 91 (Withdrawn): The method of claim 79 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 92 (Withdrawn): The method of claim 80 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and Pneumocystis carinii, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 93 (Withdrawn): The method of claim 81 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory

diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 94 (Withdrawn): The method of claim 82 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 95 (Withdrawn): The method of claim 83 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 96 (Withdrawn): The method of claim 84 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

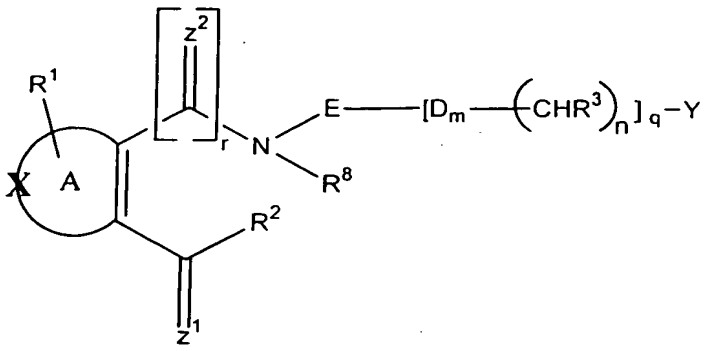
Claim 97 (Withdrawn): The method of claim 85 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 98 (Withdrawn): The method of claim 86 wherein the disease or indication is selected from the group consisting of rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

Claim 99. (New) A compound prepared by

(a) obtaining the atomic coordinates of a crystal comprising a polypeptide that contains a ubiquinone binding site of DHODH and a compound that is capable of binding to the ubiquinone binding site of DHODH which contains an aromatic or non-aromatic ring system as a core structure, a group capable of forming a hydrogen bond and/or interacting ionically with structural elements of subunits 2 or 3 of the ubiquinone binding site of DHODH and a group capable of interacting hydrophobically with structural elements of subsite 1 of the ubiquinone binding site of DHODH, with the proviso that the following compounds are excluded:

compounds of the formula



wherein

A is a non-aromatic ring containing five carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring may be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO or SO_2, and wherein one or more of the carbon atoms in the ring may carry a substituent R^1;

D is O, S, SO_2, NR^4 or CH_2;

Z^1 and Z^2 are independent from each other O, S. or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy or alkyl;

R^2 is H, OR^6 or NHR^7;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl, O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, or S-cycloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl or aryl;

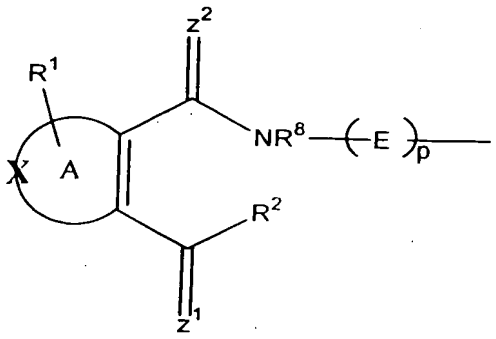
R^6 is H, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester or dialkylphosphate;

R^7 is H, alkyl, aryl, alkoxy, O-aryl, cycloalkyl or O-cycloalkyl;

R^8 is hydrogen or alkyl;

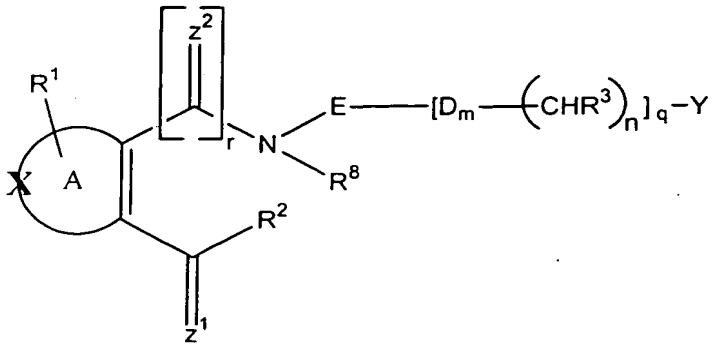
E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



m is 0 or 1, n is 0 or 1, p is 0 or 1, r is 0 or 1 and q is 0 to 10;

and compounds of the formula:



wherein

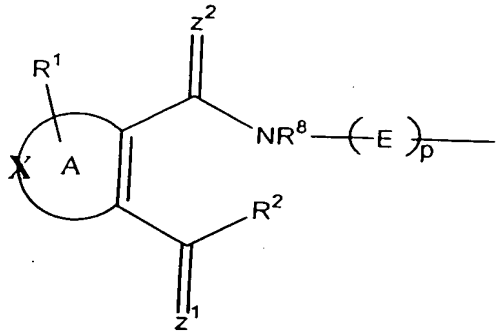
A is a non-aromatic ring containing 4, 5, 6, 7 or 8 carbon atoms, wherein the ring system

comprises at least one double bond and wherein one or more of the carbon atoms in the ring may be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO or SO_2, and wherein one or more of the carbon atoms in the ring may carry a substituent R^1;

D, Z^1, Z^2, R^1, R^3, R^4, R^5, R^6, R^8 and E are as defined above;

R^2 is H or OR^6;

Y is a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



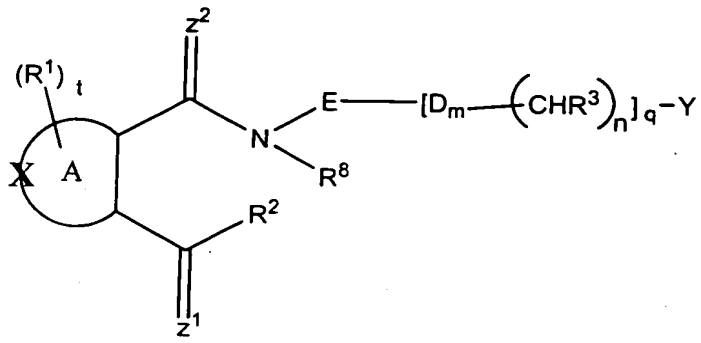
m, n, p, r, and q are as defined above;

(b) using said atomic coordinates to define the ubiquinone binding site of DHODH; and

(c) identifying a compound that fits the ubiquinone binding site of DHODH.

Claim 100. (New) A compound prepared by

(a) obtaining the atomic coordinates of a crystal comprising a polypeptide that contains a ubiquinone binding site of DHODH and a compound that is capable of binding to the ubiquinone binding site of DHODH and which has formula (I):



or salts or isomers thereof, wherein

A is a 4-8 membered non-aromatic ring system, wherein one or more of the carbon atoms in the ring may be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO or SO_2;

D is O, S, SO_2, NR^4 or CH_2;

Z^1 and Z^2 are independent from each other O, S, or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy, $-CO_2R''$, $-SO_3H$, -OH, -CONR*R", $-CR''O-$, $-SO_2NR*R''$, $-NO_2$, $-SO_2-R''$, -SO-R*, -CN, alkoxy, alkylthio, aryl, $-NR''-CO_2-R'$, -NR"-CO-R*, $-NR''-SO_2-R'$, -O-CO-R*, -NR*R", -NR*OR", $-O-CO_2-R''$, -O-CO-NR*R", cycloalkyl, alkylamino, hydroxyalkylamino, -SH, heteroaryl or alkyl;

R* independently represents H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroalkyl;

R' independently represents H, $-CO_2R''$, -CONHR", $-CR''O-$, $-SO_2NR''$, -NR"-CO-haloalkyl, $-NO_2$, $-NR''SO_2$-haloalkyl, $-NR''-SO_2$-alkyl, $-SO_2$-alkyl, NR"-CO-alkyl, -CN, alkyl, cycloalkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, -NR"R*, -NR"OR* alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R" independently represents hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl,

heteroaryl or aminoalkyl;

R^2 is H, OR^6 or NHR^7, or R^2 together with the nitrogen atom to which R^8 is attached forms a 5 or 6 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_{0-3}$ and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl, O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, or S-cycloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl or aryl;

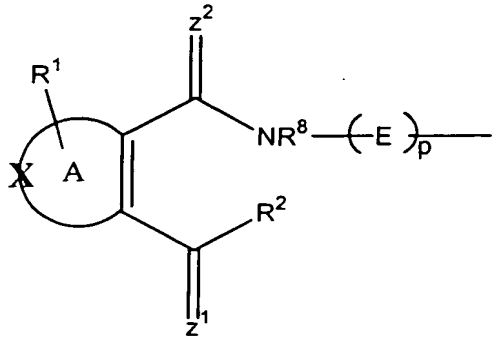
R^6 is H, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester or dialkylphosphate;

R^7 is H, alkyl, aryl, alkoxy, O-aryl, cycloalkyl or O-cycloalkyl;

R^8 is hydrogen or alkyl;

E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



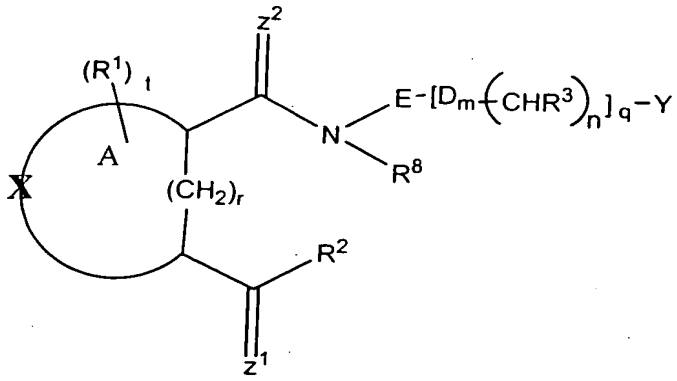
m is 0 or 1, n is 0 or 1, p is 0 or 1, q is 0 or 1 and t is 1 to 3; with the proviso that trans-2-[4-(naphthalin-2-yl)thiazol-2-ylaminocarbonyl]cyclopentane carboxylic acid is excluded;

(b) using said atomic coordinates to define the ubiquinone binding site of DHODH; and

(c) identifying a compound that fits the ubiquinone binding site of DHODH.

Claim 101. (New) A compound prepared by

(a) obtaining the atomic coordinates of a crystal comprising a polypeptide that contains a ubiquinone binding site of DHODH and a compound that is capable of binding to the ubiquinone binding site of DHODH and which has formula (II):



or salts or isomers thereof, wherein

A is a 3-8 membered non-aromatic ring system, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring may be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO, CO or SO_2, wherein, when r = 0, there is no double bond between the carbon atoms carrying the substituents $-CZ^1-$ and $-CZ^2-$;

D is O, S, SO_2, NR^4 or CH_2;

Z^1 and Z^2 are independent from each other O, S. or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy, $-CO_2R"$, $-SO_3H$, -OH, -CONR*R", -CR"O-, $-SO_2NR*R"$, $-NO_2$, $-SO_2-R"$, -SO-R*, -CN, alkoxy, alkylthio, aryl, -NR"-CO_2-R', -NR"-CO-R*, -NR"-SO_2-R', -O-CO-R*, -NR*R", -NR*OR", -O-CO_2-R", -O-CO-NR*R", cycloalkyl, alkylamino, hydroxyalkylamino, -SH, heteroaryl or alkyl;

R* independently represents H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroalkyl;

R' independently represents H, $-CO_2R"$, -CONHR", -CR"O-, $-SO_2NR"$, -NR"-CO-haloalkyl, $-NO_2$, -NR"SO_2-haloalkyl, -NR"-SO_2-alkyl, $-SO_2$-alkyl, -NR"-CO-alkyl, -CN, alkyl, cycloalkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, -NR"R*, -NR"OR*, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R" independently represents hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is H, $-OR^6$, $-NHR^7$, $-NHOR^6$, or R^2 together with the nitrogen atom to which R^8 is attached forms a 5 or 6 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_{0-3}$ and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl, O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, or S-cycloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl or aryl;

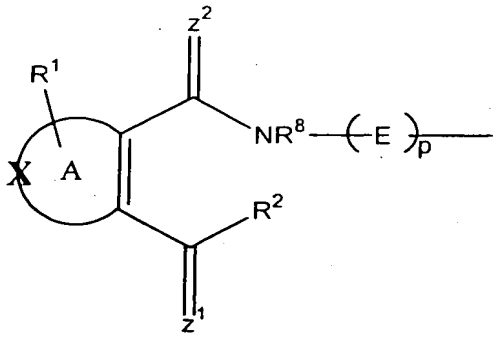
R^6 is H, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester or dialkylphosphate;

R^7 is H, alkyl, aryl, alkoxy, O-aryl, cycloalkyl or O-cycloalkyl;

R^8 is hydrogen or alkyl;

E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



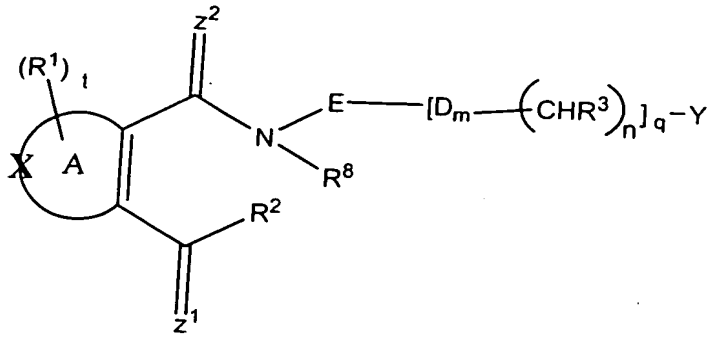
m is 0 or 1, n is 0 or 1, p is 0 or 1, r is 0 or 1, q is 0 or 1 and t is 1 to 3;

(b) using said atomic coordinates to define the ubiquinone binding site of DHODH; and

(c) identifying a compound that fits the ubiquinone binding site of DHODH.

Claim 102. (New) A compound prepared by

(a) obtaining the atomic coordinates of a crystal comprising a polypeptide that contains a ubiquinone binding site of DHODH and a compound that is capable of binding to the ubiquinone binding site of DHODH and which has formula (II):



and salts and physiologically functional derivatives thereof, wherein

A is a heteroaromatic 5-membered ring system containing one or more groups X selected from the group consisting of S, O, N, NR^4, SO and SO_2;

D is O, S, SO_2, NR^4 or CH_2;

Z^1 and Z^2 are independent from each other O, S. or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy, $-CO_2R''$, $-SO_3H$, -OH, -CONR*R", -CR"O-, $-SO_2NR*R''$, $-NO_2$, $-SO_2-R''$, -SO-R*, -CN, alkoxy, alkylthio, aryl, $-NR''-CO_2-R'$, -NR"-CO-R*, $-NR''-SO_2-R'$, $-O-CO-R*$, $-O-CO_2-R*$, -O-CO-NR*R", cycloalkyl, alkylamino, hydroxyalkylamino, -SH, heteroaryl or alkyl;

R* independently represents H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroalkyl;

R' independently represents H, $-CO_2R''$, -CONHR", -CR"O-, $-SO_2NR''$, -NR"-CO-haloalkyl, $-NO_2$, $-NR''SO_2$-haloalkyl, $-NR''-SO_2$-alkyl, $-SO_2$-alkyl, -NR"-CO-alkyl, -CN, alkyl, cycloalkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R" independently represents hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is H, $-OR^6$, $-NHR^7$, $-NR^7 OR^7$, or R^2 together with the nitrogen atom to which R^8 is attached forms a 5 or 6 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_{0-3}$ and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl, O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, S-cycloalkyl, arylalkyl or haloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl or aryl;

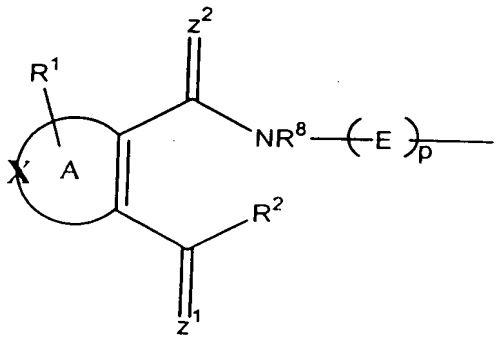
R^6 is H, alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester or dialkylphosphate;

R^7 is H, -OH, alkyl, aryl, alkoxy, O-aryl, cycloalkyl or O-cycloalkyl;

R^8 is hydrogen or alkyl;

E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



m is 0 or 1, n is 0 or 1, p is 0 or 1, q is 0 or 1, s is 0 to 2 and t is 0 to 3; with the proviso that the following compounds are excluded:

compounds wherein ring A contains five atoms, $Z^1=Z^2=O$, and R^2 together with the nitrogen atom which is attached to R^8 forms a 5 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_8$, R^8 is absent and s is 0;

compounds wherein ring A contains three carbon atoms and two nitrogen atoms, $Z^1=Z^2=O$, and R^2 together with the nitrogen atom which is attached to R^8 forms a 5 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_8$, R^8 is absent and s is 0;

4-[4-(naphthalin-2-yl)thiazol-2-ylaminocarbonyl]furan-3-carboxylic acid; and

5-[4-(naphthalin-2-yl)thiazol-2-ylaminocarbonyl]-2H-[1,2,3]-triazole-4-carboxylic acid;

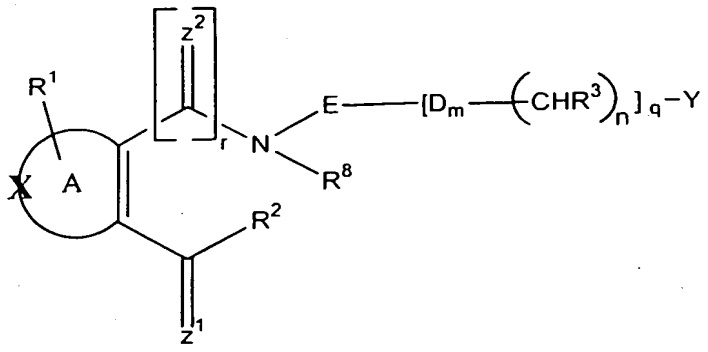
(b) using said atomic coordinates to define the ubiquinone binding site of DHODH; and

(c) identifying a compound that fits the ubiquinone binding site of DHODH.

Claim 103. (New) A compound prepared by

(a) obtaining the atomic coordinates of a crystal comprising a polypeptide that contains a ubiquinone binding site of DHODH and a compound that is capable of binding to the ubiquinone binding site of DHODH which contains an aromatic or non-aromatic ring system as a core structure, a group capable of forming a hydrogen bond and/or interacting ionically with structural elements of subunits 2 or 3 of the ubiquinone binding site of DHODH and a group capable of interacting hydrophobically with structural elements of subsite 1 of the ubiquinone binding site of DHODH, with the proviso that the following compounds are excluded:

compounds of the formula



wherein

A is a non-aromatic ring containing five carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring may be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO or SO_2, and wherein one or more of the carbon atoms in the ring may carry a substituent R^1;

D is O, S, SO_2, NR^4 or CH_2;

Z^1 and Z^2 are independent from each other O, S. or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy or alkyl;

R^2 is H, OR^6 or NHR^7;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl, O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, or S-cycloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl or aryl;

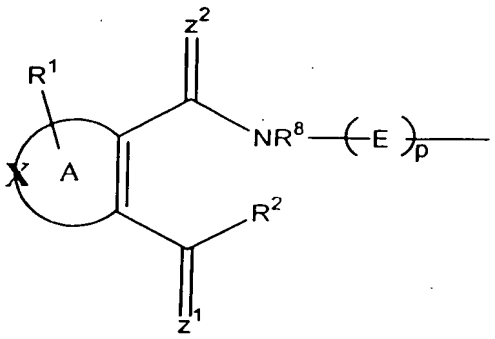
R^6 is H, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester or dialkylphosphate;

R^7 is H, alkyl, aryl, alkoxy, O-aryl, cycloalkyl or O-cycloalkyl;

R^8 is hydrogen or alkyl;

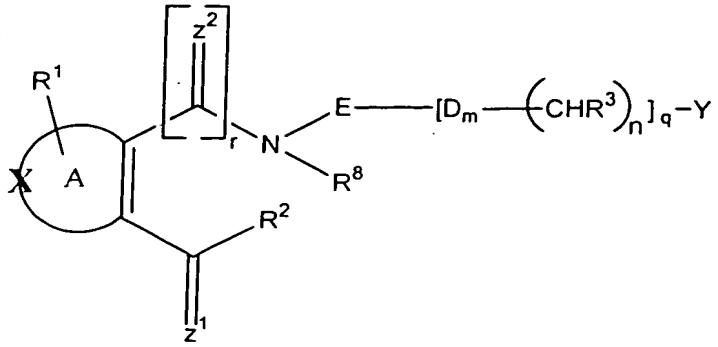
E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



m is 0 or 1, n is 0 or 1, p is 0 or 1, r is 0 or 1 and q is 0 to 10;

and compounds of the formula:



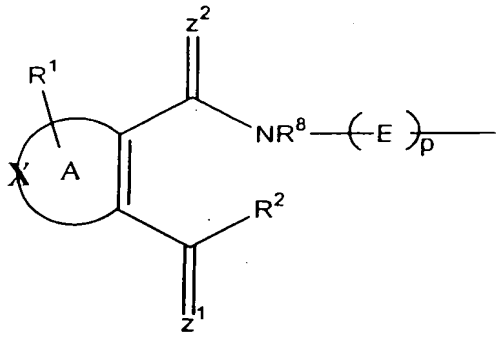
wherein

A is a non-aromatic ring containing 4, 5, 6, 7 or 8 carbon atoms, wherein the ring system comprises at least one double bond and wherein one or more of the carbon atoms in the ring may be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO or SO_2, and wherein one or more of the carbon atoms in the ring may carry a substituent R^1;

D, Z^1, Z^2, R^1, R^3, R^4, R^5, R^6, R^8 and E are as defined above;

R^2 is H or OR^6;

Y is a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



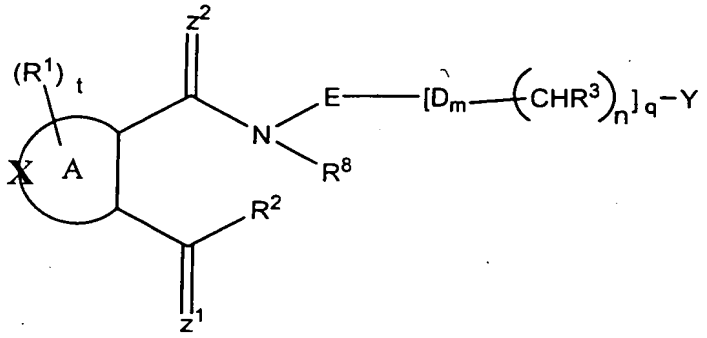
m, n, p, r, and q are as defined above;

(b) using said atomic coordinates to define the structural requirements of the inhibitor contained in the polypeptide-inhibitor complex; and

(c) designing a compound on the basis of said structural requirements.

Claim 104. (New) A compound prepared by

(a) obtaining the atomic coordinates of a crystal comprising a polypeptide that contains a ubiquinone binding site of DHODH and a compound that is capable of binding to the ubiquinone binding site of DHODH and which has formula (I):



or salts or isomers thereof, wherein

A is a 4-8 membered non-aromatic ring system, wherein one or more of the carbon atoms in the ring may be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO or SO_2;

D is O, S, SO_2, NR^4 or CH_2;

Z^1 and Z^2 are independent from each other O, S. or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy, $-CO_2R''$, $-SO_3H$, -OH, -CONR*R", -CR"O-, $-SO_2NR*R''$, $-NO_2$, $-SO_2-R''$, -SO-R*, -CN, alkoxy, alkylthio, aryl, $-NR''-CO_2-R'$, -NR"-CO-R*, $-NR''-SO_2-R'$, -O-CO-R*, -NR*R", -NR*OR", $-O-CO_2-R*$, -O-CO-NR*R", cycloalkyl, alkylamino, hydroxyalkylamino, -SH, heteroaryl or alkyl;

R* independently represents H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroalkyl;

R' independently represents H, $-CO_2R''$, -CONHR", -CR"O-, $-SO_2NR''$, -NR"-CO-haloalkyl, $-NO_2$, $-NR''SO_2$-haloalkyl, $-NR''-SO_2$-alkyl, $-SO_2$-alkyl, NR"-CO-alkyl,

-CN, alkyl, cycloalkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, -NR"R*, -NR"OR*, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R" independently represents hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is H, OR^6 or NHR^7, or R^2 together with the nitrogen atom to which R^8 is attached forms a 5 or 6 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_{0-3}$ and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl, O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, or S-cycloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl or aryl;

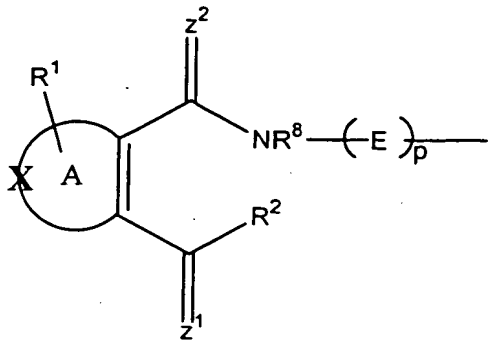
R^6 is H, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester or dialkylphosphate;

R^7 is H, alkyl, aryl, alkoxy, O-aryl, cycloalkyl or O-cycloalkyl;

R^8 is hydrogen or alkyl;

E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



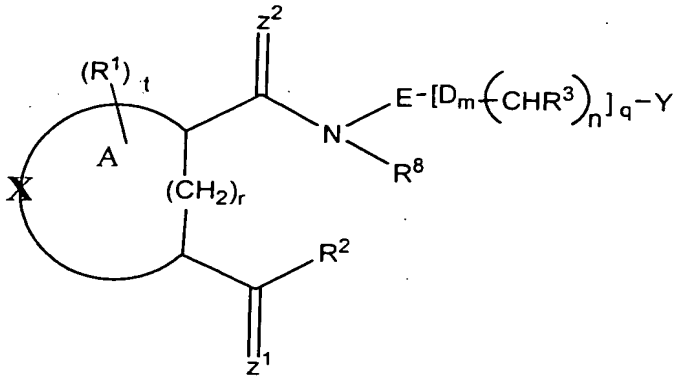
m is 0 or 1, n is 0 or 1, p is 0 or 1, q is 0 or 1 and t is 1 to 3; with the proviso that trans-2-[4-(naphthalin-2-yl)thiazol-2-ylaminocarbonyl]cyclopentane carboxylic acid is excluded;

(b) using said atomic coordinates to define the structural requirements of the inhibitor contained in the polypeptide-inhibitor complex; and

(c) designing a compound on the basis of said structural requirements.

Claim 105. (New) A compound prepared by

(a) obtaining the atomic coordinates of a crystal comprising a polypeptide that contains a ubiquinone binding site of DHODH and a compound that is capable of binding to the ubiquinone binding site of DHODH and which has formula (II):



or salts or isomers thereof, wherein

A is a 3-8 membered non-aromatic ring system, wherein the ring system comprises at

least one double bond and wherein one or more of the carbon atoms in the ring may be replaced by a group X, wherein X is selected from the group consisting of S, O, N, NR^4, SO or SO_2, wherein, when r = 0, there is no double bond between the carbon atoms carrying the substituents $-CZ^1-$ and $-CZ^2-$;

D is O, S, SO_2, NR^4 or CH_2;

Z^1 and Z^2 are independent from each other O, S. or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy, $-CO_2R''$, $-SO_3H$, -OH, -CONR*R", -CR"O-, $-SO_2NR*R''$, $-NO_2$, $-SO_2-R''$, -SO-R*, -CN, alkoxy, alkylthio, aryl, $-NR''-CO_2-R'$, -NR"-CO-R*, $-NR''-SO_2-R'$, -O-CO-R*, -NR*R", -NR*OR", $-O-CO_2-R*$, -O-CO-NR*R", cycloalkyl, alkylamino, hydroxyalkylamino, -SH, heteroaryl or alkyl;

R* independently represents H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroalkyl;

R' independently represents H, $-CO_2R''$, -CONHR", -CR"O-, $-SO_2NR''$, -NR"-CO-haloalkyl, $-NO_2$, $-NR''SO_2$-haloalkyl, $-NR''-SO_2$-alkyl, $-SO_2$-alkyl, -NR"-CO-alkyl, -CN, alkyl, cycloalkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, -NR"R*, -NR"OR*, alkylthio, hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R" independently represents hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is H, $-OR^6$, $-NHR^7$, -NH OR^6, or R^2 together with the nitrogen atom to which R^8 is attached forms a 5 or 6 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_{0-3}$ and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl, O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyl, haloalkyloxy,

heteroaryl, alkylthio, S-aryl, or S-cycloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl or aryl;

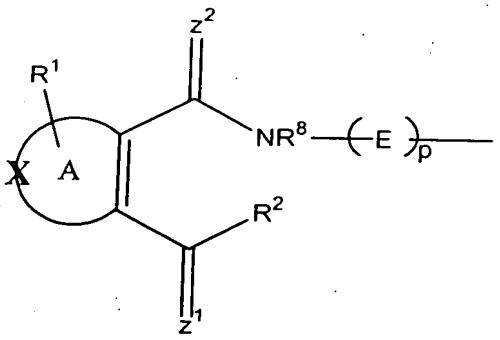
R^6 is H, alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester or dialkylphosphate;

R^7 is H, alkyl, aryl, alkoxy, O-aryl, cycloalkyl or O-cycloalkyl;

R^8 is hydrogen or alkyl;

E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



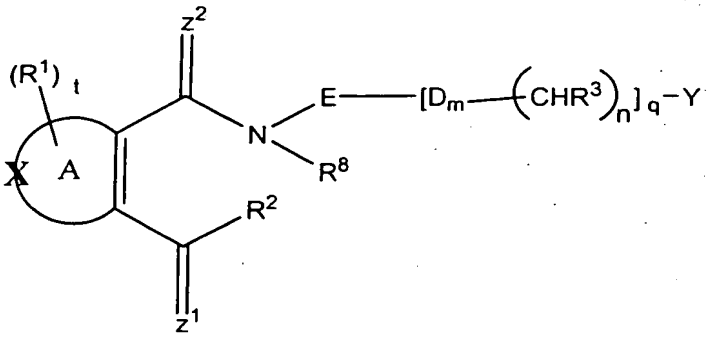
m is 0 or 1, n is 0 or 1, p is 0 or 1, r is 0 or 1, q is 0 or 1 and t is 1 to 3;

(b) using said atomic coordinates to define the structural requirements of the inhibitor contained in the polypeptide-inhibitor complex; and

(c) designing a compound on the basis of said structural requirements.

Claim 106. (New) A compound prepared by

(a) obtaining the atomic coordinates of a crystal comprising a polypeptide that contains a ubiquinone binding site of DHODH and a compound that is capable of binding to the ubiquinone binding site of DHODH and which has formula (II):



and salts and physiologically functional derivatives thereof, wherein

A is a heteroaromatic 5-membered ring system containing one or more groups X selected from the group consisting of S, O, N, NR^4, SO and SO_2;

D is O, S, SO_2, NR^4 or CH_2;

Z^1 and Z^2 are independent from each other O, S. or NR^5;

R^1 is independently H, halogen, haloalkyl, haloalkyloxy, $-CO_2R''$, $-SO_3H$, -OH, -CONR*R", -CR"O-, $-SO_2NR*R''$, $-NO_2$, $-SO_2-R''$, -SO-R*, -CN, alkoxy, alkylthio, aryl, $-NR''-CO_2-R'$, -NR"-CO-R*, $-NR''-SO_2-R'$, -O-CO-R*, $-O-CO_2-R''$, -O-CO-NR*R", cycloalkyl, alkylamino, hydroxyalkylamino, -SH, heteroaryl or alkyl;

R* independently represents H, alkyl, cycloalkyl, aminoalkyl, alkoxy, -OH, -SH, alkylthio, hydroxyalkyl, haloalkyl, haloalkyloxy, aryl or heteroalkyl;

R' independently represents H, $-CO_2R''$, -CONHR", -CR"O-, $-SO_2NR''$, -NR"-CO-haloalkyl, $-NO_2$, $-NR''SO_2$-haloalkyl, $-NR''-SO_2$-alkyl, $-SO_2$-alkyl, -NR"-CO-alkyl, -CN, alkyl, cycloalkyl, aminoalkyl, alkylamino, alkoxy, -OH, -SH, alkylthio,

hydroxyalkyl, hydroxyalkylamino, halogen, haloalkyl, haloalkyloxy, aryl, arylalkyl or heteroaryl;

R" independently represents hydrogen, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl or aminoalkyl;

R^2 is H, $-OR^6$, $-NHR^7$, $-NR^7 OR^7$, or R^2 together with the nitrogen atom to which R^8 is attached forms a 5 or 6 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_s$ and R^8 is absent;

R^3 is H, alkyl, cycloalkyl, aryl, arylalkyl, alkoxy, O-aryl, O-cycloalkyl, halogen, aminoalkyl, alkylamino, hydroxylamino, hydroxylalkyl, haloalkyloxy, heteroaryl, alkylthio, S-aryl, S-cycloalkyl, arylalkyl or haloalkyl;

R^4 is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkoxy, O-aryl, alkyl or aryl;

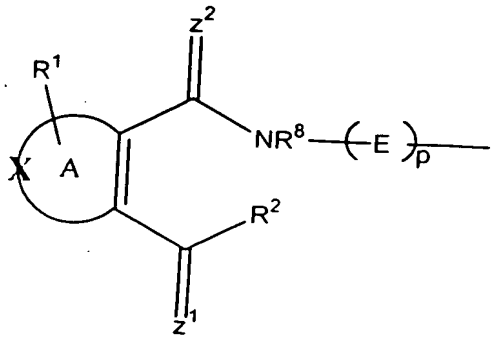
R^6 is H, alkyl, cycloalkyl, aryl, arylalkyl, heteroalkyl, alkylaryl, alkoxyalkyl, acylmethyl, (acyloxy)alkyl, non-symmetrical (acyloxy)alkyldiester or dialkylphosphate;

R^7 is H, -OH, alkyl, aryl, alkoxy, O-aryl, cycloalkyl or O-cycloalkyl;

R^8 is hydrogen or alkyl;

E is an alkyl or cycloalkyl group or a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring;

Y is hydrogen, halogen, haloalkyl, haloalkyloxy, alkyl, cycloalkyl, a monocyclic or polycyclic substituted or unsubstituted ring system which may contain one or more groups X and which contains at least one aromatic ring or



m is 0 or 1, n is 0 or 1, p is 0 or 1, q is 0 or 1, s is 0 to 2 and t is 0 to 3; with the proviso that the following compounds are excluded:

compounds wherein ring A contains five atoms, $Z^1=Z^2=0$, and R^2 together with the nitrogen atom which is attached to R^8 forms a 5 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_s$, R^8 is absent and s is 0;

compounds wherein ring A contains three carbon atoms and two nitrogen atoms, $Z^1=Z^2=0$, and R^2 together with the nitrogen atom which is attached to R^8 forms a 5 membered heterocyclic ring with the proviso that R^2 is $-[CH_2]_s$, R^8 is absent and s is 0;

4-[4-(naphthalin-2-yl)thiazol-2-ylaminocarbonyl]furan-3-carboxylic acid; and

5-[4-(naphthalin-2-yl)thiazol-2-ylaminocarbonyl]-2H-[1,2,3]-triazole-4-carboxylic acid;

(b) using said atomic coordinates to define the structural requirements of the inhibitor contained in the polypeptide-inhibitor complex; and

(c) designing a compound on the basis of said structural requirements.